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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/622,613	07/31/2001	Susanna M. Rybak	15280-3431US	8380

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Kenneth A Weber
Townsend & Townsend & Crew
Two Embarcadero Center 8th Floor
San Francisco, CA 94111-3834

EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/622,613	RYBAK ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,20-27,31-39,41 and 42* is/are pending in the application.

4a) Of the above claim(s) *20-27 and 31-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16, 34-39, 41, and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Seq. Alignment

DETAILED ACTION

Election/Restrictions

Receipt of a new sequence listing along with the new CFR filed on 11/06/06 is acknowledged.

Claims 20- 27, and 31-33 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-16, 20-27, 31-39, 41, and 42 are pending and claims 1-16, 34-39, 41, and 42 are examined on merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

This Office action contains new grounds of rejection.

Claim Objections, Maintained for Claim 6

Claim 6 remain objected under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

This rejection is maintained because applicant does not argue with the Office's interpretation of instant claims 1-16 (see page 4, lines 8-12 of the Office action mailed on 7/3/2003). The base claim says that the instantly claimed ribonuclease has glutamine with three other recited amino acids at the recited positions. However, the ribonuclease in instant claim 6 does not have glutamine at position 1 as required in the base claim the instant claim depends on.

Although applicant has not addressed the Office's objection of the claims, Objection of all other claims set forth in the Office action mailed on 7/3/2003 will

be withdrawn because there is some ambiguity in the specification in terms of whether position 1 means position –1. Therefore other objected claims will be rejected under 35 U.S.C. 112, second paragraph. See new grounds of rejection below.

Claim Rejections - 35 USC § 112, Maintained

Claim Rejections - 35 USC § 112

Claims 1-16 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are interpreted as drawn to ribonucleases with glutamine at position 1 with substantial identity to SEQ ID NO:2.

Applicant argues that it is routine in biotechnology art to screen enzyme for its activity. This argument has been fully considered but found unpersuasive because there is still a great deal of unpredictability in ONCONASE related ribonuclease in terms of what amino acid is in position 1. The specification at page 44 lines 20-23 teaches that that N-terminal pyroglutamic acid is critical for activity. However, instantly claimed ribonuclease has glutamine at its N-terminus. Newton et al (1998, Biochemistry vol. 37, pages 5173-83) and Newton et al (1997, Protein Engineering, vol. 10, pages 463-70) teach that position 1 of ribonuclease is important for its activity and ribonuclease activity has to be determined experimentally when the position 1 is replaced with something else.

Further, the specification is not clear about recombinant Onconase in Table 1 is same as the recombinant Onconoase, the first two words of line 20 of the specification. If those two are the same, it the seems to be discrepancy between the disclosures of the instant specification at Table 1 and lines 20-23 of page 44, and that of Newton et al (1997, Protein Engineering, vol. 10, pages 463-70). The instant specification at Table 1 appears to say that position 1 (Q, One letter symbol for glutamine) of the recombinant Onconase disclosed in Newton et al (1997, Protein Engineering, vol. 10, pages 463-70) is replaced S (Serine). However, Newton et al (1997) at Table 1 does not teach any construction of such recombinant ribonuclease. For example, instant claim 2 has methionine at position 1 and the art teaches that ribonuclease with methione at position 1 do not have activity. Note the first line of the abstract by Newton et al (1998, Biochemistry vol. 37, pages 5173-83). Newton et al (1998, Biochemistry vol. 37, pages 5173-83) at Fig. 2 teaches only certain amino acid at position 1 works i.e. [Met(-1)]E1S and [Met(-1)] E1Y have ribonuclease activity. Note Table 2. Further, sequence search of SEQ ID NO:2 reveals that instant SEQ ID NO:2 is a truncated **putative** ribonuclease according to Chen et al (Nucleic Acids Res. 2000 Jun 15; 28(12): 2375-82). Note the attached sequence alignment of instant SEQ ID NO:2 to the protein sequence of Q918V8 from Sptrembl data base. Based on the limited guidance and no working examples in the specification, as well as unpredictability in ONCONASE-related ribonuclease enzymatic activity in terms of the N-terminus amino acid identity, it is concluded that undue experimentation is required to practice the instantly claimed invention.

The Following are New Grounds of Objections and Rejections

Specification

The use of the trademark ONCONASE has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology. Note the specification at page 2 line 3, for example. Applicant is kindly requested to go over the entire specification very carefully and to change any occurrence of "Onconase" to "ONCONASE"

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The disclosure is objected to because the specification at page 2 line 10 says that **ONCONASE with a N-terminal glutamine**. However, Ardelt et al (J. Biol. Chem. vol. 266, pages 245-251) teach at Fig.3 at page 247 that ONCONASE isolated from Rana pipiens is **glutamic acid**.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "substantial identity" but it is not clear what the metes and bounds are.

Claims 1-16 is also confusing because the base claim 1 says that the instantly claimed ribonuclease begins with gluatmine at its N-terminus "an amino terminal end beginning with a glutamine", which appears to mean that position 1 of the claimed ribonuclease must have glutamine at position 1. However, the dependent claims 2, 4, 8, and 10 say different residues are at position 1. The specification at page 40 line 15 says that an extra methionine at the amino terminal end [Met-(-1)] could be added as fusion protein. It is not clear whether the limitation "an amino terminal end beginning with a glutamine" means glutamine at position 1 or means something else. This rejection affects all claims depend from claim 1 or claims 2, 4, 8, and 10.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **written description** requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a genus of a riboncluease comprising something substantial identity to SEQ ID NO:2 with four specified amino acid at position 1, 11, 21, and 103.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying

characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure (SEQ ID NO:2, 104 amino acids) of an 127-amino acid putative ribonuclease according to Chen et al (cited above). Note the attached sequence alignment of instant SEQ ID NO:2 with that disclosed in Chen at al (cited above). Chen et al (which was published after the effective filing date of instant application) teach that even the full length protein (23 more amino acids at its N-terminus than instant SEQ ID NO:2) comprising instant SEQ ID NO:2 is a putative ribonuclease. However, instant claims also encompass the 127-amino acid putative ribonuclease disclosed in Chen et al, which the instant specification fails to describe. Further, there is not even identification of any particular portion of the structure that must be conserved. It appears applicant did not have possession of the full length protein sequence comprising instant SEQ ID NO:2 at the time the instant application was filed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the

art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, given that the specification has only described SEQ ID NO: 2. Therefore, only isolated polypeptides **consisting** the amino acid sequence set forth in SEQ ID NO: 2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is separable from its enablement provision (see page 1115).

A definition by function alone "does not suffice, to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." *Eli Lily*, 119 F.3 at 1568, 43 USPQ2d at 1406.

Claims 5 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **enablement** requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are drawn to a ribonuclease with cyclized derivative of glutamic acid "pyroglutamic acid" at its N-terminus. The specification at page 7 shows the structure of pyroglutamic acid, which is the cyclized internal amide of **glutamic acid**, not glutamine. Glutamine structure disclosed at page 61, 4th row in Voet et al (1990, Biochemistry, John Wiles & Sons, page 61 only) indicates that cyclized internal

amide of glutamine would not result in pyroglutamic acid. Further, US Pat. 5,728,805 at the paragraph bridging columns 9-10 teaches that ribonuclease from Rana pipiens with 96. 5% sequence identity to instant SEQ ID NO:2 has glutamic acid at position 1, which is cyclized to pyroglutamic acid in its native form. Further, Joshi et al (J Pharm Sci. 2002 Nov; 91(11): 2331-45) teach that cyclization of glutamine leads to formation of imide, not pyroglutamic acid (see abstract, Table 1, row 7, column 4). However, the specification at numerous places, for example, at page 3 line 5 page 29 lines 16-26, asserts that cyclization of glutamine would result in the instantly claimed structures. Applicant is invited to provide the chemical reaction necessary in order to convert glutamine to pyroglutamic acid in order to obviate this rejection.

Claims 34-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are interpreted as drawn to pharmaceutical comprising SEQ ID NO: 2, 4, 6, 8, 11, 13, 15, 17, 19, 21, 24 or 26 alone (claims 34 and 37), or other art-known antineoplastic agents (claims 35-36) or method of killing cancer cells either with any of SEQ ID NO: 2, 4, 6, 8, 11, 13, 15, 17, 19, 21, 24 or 26 alone (claims 38) or SEQ ID NO: 2, 4, 6, 8, 11, 13, 15, 17, 19, 21, 24 or 26 linked to other ligand binding moiety (claims 39, 41, and 42).

This rejection is made because the specification at page 1, second paragraph discloses that the trademark name ONCONASE is isolated from Rana pipiens by Ardelt et al (J. Biol. Chem. vol. 266, pages 245-251). The specification also says at page 2 line that expression of active recombinant ONCONASE has been problematic because ONCONASE requires a pyroglutamic acid at the N-terminus for its activity and "**ONCONASE with a N-terminal glutamine**" is not expressed by bacteria very well.

Ardelt et al (J. Biol. Chem. vol. 266, pages 245-251) teach at Fig.3 at page 247 that ONCONASE isolated from Rana pipiens is glutamic acid (Glu, E), not glutamine and US Pat. 5,728,805 (cited above) also teaches at the paragraph bridging columns 9-10 teaches that ribonuclease from Rana pipiens with 96. 5% sequence identity to instant SEQ ID NO:2 has glutamic acid at position 1, which is cyclized to pyroglutamic acid in its native form. Based on the teachings of the Newton et al (1998, Biochemistry vol. 37, pages 5173-83) at the two lines of the abstract teach that adding one methionine to ONCOSE in order to better express it in E. coli result in "little enzymatic activity or cytotoxic activity" and the teaching of the instant application at pages 1-2, N-terminal residue is critical for the ribonuclease activity and its associated anti-tumor activity. The specification does not teach instant claimed product with glutamine at position 1 has any ribonuclease and/or cytotoxic activity. Newton et al (1998, Biochemistry vol. 37, pages 5173-83, note that the article was published around the time the instant application has been filed) et al teach even single amino acid change at the N-

terminus of a recombinant cytotoxic ribonuclease markedly influence biochemical and biological properties. Note the title.

Considering unpredictability of a recombinant cytotoxic ribonuclease with change at N-terminus and no working example that the instantly claimed product has any cytotoxic ribonuclease activity, along with no working example in the specification, it is concluded that one skilled in the art would have difficulty accepting efficacy of instantly claimed product as a pharmaceutical.

Double Patenting

Applicant is advised that should claim 34 be found allowable, claim 37 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 34 calls all of the Markush group alternative represented as SEQ ID NOs as a ribonuclease while claim 37 call the same entity as a cytotoxic reagent.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne C Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu

January 26, 2004